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| EXAMINER |
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GOLDBERG, JEANINE ANNE

| ART UNIT | PAPER NUMBER |
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1634

DATE MAILED: 03/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

SM

Office Action Summary**Application No.**

09/954,586

Applicant(s)

CUNNINGHAM ET AL.

Examiner

Jeanine A Goldberg

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 December 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 11, 12, 14-23, 29, 37-40, 50-53, 59, 60, 84 and 87-159 is/are pending in the application.
- 4a) Of the above claim(s) 87-92, 100-105, 108-113, 127-132 and 145-150 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 11-23, 29, 37-40, 50-53, 59, 60, 84, 93-99, 106, 107, 114-126, 133-144 and 151-159 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date <u>104</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. This action is in response to the papers filed December 19, 2002. Currently, claims 1, 11-12, 14-23, 29, 37-40, 50-53, 59-60, 84, 87-159 are pending.
2. Claims 87-92, 100-105, 108-113, 127-132, 145-150 are withdrawn from consideration, as drawn to non-elected subject matter.

Election/Restrictions

3. Applicant's election without traverse of SEQ ID NO: 6, 10, 14, 18, 29, 33, 37, 41, 48, 54, 60, 66 in Paper filed December 19, 2002 is acknowledged.

The response did not traverse the restriction or election requirement, therefore, arguing the restriction requirement at this time is inappropriate. However, the response argues that SEQ ID NO: 6 and SEQ ID NO: 5 are related and such the broader should be examined. This is not appropriate argument, as broader claims are often not allowable, whereas narrower claims are. Moreover, SEQ ID NO: 5 does not appear to be within the scope of claim 1 because the claim has been amended to require that the probe does not comprise a base region in addition to said target binding region that is cable of stably binding to said target. Therefore, SEQ ID NO: 5 has been excluded from Claim 1.

Priority

4. This application claims priority to U.S. Provisional Application No. 60/232,028, filed September 12, 2000.

Drawings

5. The drawings are acceptable.

Specification

6. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

For example, page 31, contains a hyperlink.

Response to Arguments

The MPEP provides that "Where the hyperlinks and/or other forms of browser-executable codes are part of applicant's invention and it is necessary to have them included in the patent application in order to comply with the requirements of 35 U.S.C. 112, first paragraph, and applicant does not intend to have these hyperlinks be active links, examiners should not object to these hyperlinks." The instant application does not appear to require that the hyperlink is required in order to comply with 112/1st. In the event that applicant wishes to include the website, applicant is requested to remove the browse executable code.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1, 14, 19-23, 29, 37-40, 50-53, 59-60, 84, 93-99, 106-107, 114-126, 133-144, 150-159 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhu et al. (J. of Infectious Disease, Vol. 177, pages 1443-1446, 1998) in view of Williams et al. (US Pat. 6,146,855, November 14, 2000) and Xiao et al. (Applied and Environmental Microbiology, Vol. 65, No. 8, pages 3386-3391, August 1999) in view of Hogan (US Pat. 5,595,874, January 1997).

The broad product claims have also been rejected in this 103 rejection in the event that the claims were amended to narrow the claims to recite consisting of SEQ ID NO: 1, 21, 22, for example.

Zhu et al. (herein referred to as Zhu) teaches a method of detecting *Cryptosporidium* using genus specific primers from the 18S rRNA. The target DNA for PCR was the small subunit rRNA gene (srDNA).

Zhu does not specifically teach using SEQ ID NO: 6 as a target sequence for the probes and primers.

However, Williams et al. (herein referred to as Williams) provides an alignment for the relatedness in Figure 3A between *C. parvum*, *C. muris*, *C. baileyi*. The positions of specific *C. parvum* 18S rRNA probes in respect of the whole 18S rRNA sequence is illustrated. SEQ ID NO: 6, 29, 48 are embedded within the sequences.

Moreover, Xiao et al. (herein referred to as Xiao) teaches a comparison study of seven *Cryptosporidium* various isolates from various hosts. The species include *C. parvum*, *C. wrairi*, *C. muris* and *C. baileyi*. Xiao teaches that the nucleotide sequences of the parasites were deposited in GenBank under various accession numbers. Xiao teaches aligning the sequences and identifying differences among the isolates.

Moreover, Hogan teaches a method which compares one or more sequence rRNA variable regions from a target organism to one or more rRNA variable region sequences from closely related species that can be utilized to distinguish between such organisms. Hogan teaches the use of specific primers col. 6-7, lines 50-67, lines 1-12, and furthermore provides specific guidance for the selection of primers,

"Once the variable regions are identified, the sequences are aligned to reveal areas of maximum homology or 'match'. At this point, the sequences are examined to identify potential probe regions. Two important objectives in designing a probe are to maximize homology to the target sequence(s) (greater than 90% homology is recommended) and to minimize homology to non-target sequence(s) (less than 90% homology to non-targets is recommended). We

have identified the following useful guidelines for designing probes with the desired characteristics.

First, probes should be positioned so as to minimize the stability of the probe:nontarget nucleic acid hybrid. This may be accomplished by minimizing the length of perfect complementarity to non-target organisms, avoiding G and C rich regions of homology to non-target sequences, and by positioning the probe to span as many destabilizing mismatches as possible (for example, dG:rU base pairs are less destabilizing than some others). Second, the stability of the probe:target nucleic acid hybrid should be maximized. This may be accomplished by avoiding long A and T rich sequences, by terminating the hybrids with G:C base pairs and by designing the probe with an appropriate T_m . The beginning and end points of the probe should be chosen so that the length and %G and %C result in a T_m about 2-10°C higher than the temperature at which the final assay will be performed. The importance and effect of various assay conditions will be explained further herein. Third, regions of the rRNA which are known to form strong structures inhibitory to hybridization are less preferred. Finally, probes with extensive self complementarity should be avoided."

Hogan teaches that "while oligonucleotide probes of different lengths and base composition may be used, oligonucleotide probes preferred in this invention are between about 15 and about 50 bases in length" (col. 10, lines 13-15)(limitations of Claims 4-6). Oligonucleotides complementary to sequences adjacent to the probe regions were synthesized and used in the hybridization mix according to Hogan et al., U.S. Pat. No. 5,030,557; filed Nov. 24, 1987, entitled "Means and Method for Enhancing Nucleic Acid Hybridization (the "helper " patent application). Hogan teaches that oligonucleotide probes may be labeled by any of several well known methods such as radioisotopes, non-radioactive reporting groups, non-isotopic materials such as fluorescent molecules (col. 10, lines 45-60). Hogan teaches that probes may be labeled using a variety of labels, as described within, and may be incorporated into diagnostic kits(limitations of Claims 74, 88, 135-155).

Therefore, it would have been *prima facie* obvious to one of ordinary skill at the time the invention was made to have modified the genus specific PCR primers taught by Zhu using the alignment provided by Williams and Xiao and the specific guidance provided by Hogan to obtain the invention as a whole. In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, however, the court stated

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent functional equivalents of the probes and primers of Zhu, a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited reference in the absence of secondary considerations. The specific probes are considered to be functionally equivalent to those of Zhu because they are located within the same region, namely the 18S rRNA as the instantly claimed oligonucleotides and those of Zhu and further because Zhu teaches the usefulness of the 18S region for detecting and distinguishing between *C. parvum*, *C. muris*, *C. baileyi* and *C. wrairi*. The art also teaches that one of skill in the art can modify the disclosed genus specific primer to enhance the properties based on factors such as probe length, melting temperature, and sequence content. Additionally, at the time the invention was

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made, the sequence of the *Cryptosporidium* nucleic acids of distinct types were known and it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made and within the skill of the art to obtain the instantly claimed oligonucleotides following the teachings of Hogan as to the identification of sequences that are genus specific and thus useful for the identification of *Cryptosporidium* by hybridization. Further, the teachings of Zhu, Williams, Xiao and Hogan indicate that the state of the art at the time the invention was made would have led one of ordinary skill in the art to the claimed genus-specific probes because Zhu, Williams, Xiao and Hogan teaches the usefulness of the 18S region of the *Cryptosporidium* for species-specific probes, species-specific primers and further teaches methods in which the probes may be modified.

Response to Arguments

The response traverses the rejection. The response asserts that if anything, Zhu and Williams would have motivated those skilled in the art to find additional probe targets within the regions amplified by Zhu. This argument has been thoroughly reviewed, but is not found persuasive because the teachings of Williams is not limited to only the regions amplified by Zhu. Zhu provides the general motivation to make genus and species specific primers and probes, Williams provides an alignment and disclosure. Thus, the ordinary artisan would have a reasonable expectation of success of obtaining additional probes from within the alignment provided by Williams. Thus, for the reasons provided above, the ordinary artisan would have designed additional species specific probes using the teachings in the art at the time the invention was

made. Thus for the reasons above and those already of record, the rejection is maintained.

9. Claims 11-13, 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhu et al. (J. of Infectious Disease, Vol. 177, pages 1443-1446, 1998) in view of Williams et al. (US Pat. 6,146,855, November 14, 2000) and Xiao et al. (Applied and Environmental Microbiology, Vol. 65, No. 8, pages 3386-3391, August 1999) in view of Hogan (US Pat. 5,595,874, January 1997) as applied to Claims 1, 6-10, 14, 19-23, 29, 37-40, 50-53, 59-60, 84, 93-99, 106-107, 114-126, 133-144, 150-159 above, and further in view of Becker et al. (US Pat. 6,361,945, March 26, 2002).

Neither Zhu, Williams, Xiao or Hogan specifically teach a method using interacting labels including luminescent label and quencher labels.

However, Becker teaches a method of using "molecule torches" for detecting the presence of a target nucleic acid sequence. Becker teaches the molecular torches contain a target binding domain, a target closing domain and a joining region (col. 2, lines 15-25). The target binding domain is biased towards the target sequence. A luminescent/quencher pair is preferably used (col. 9, lines 45-60)(limitations of Claims 11-12). Moreover, Becker teaches using 2'-methoxy substituted ribonucleotides (col. 10, lines 55-65)(limitations of Claim 13). Becker teaches "one of the advantages of using the present invention in conjunction with a transcription-associated amplification is that the molecular torch can be added prior to amplification, and detection can be

carried out without adding additional reagents (col. 12, lines 10-20). Becker teaches using pseudo peptide backbones (col. 8)(limitations of Claim 14).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the PCR detection assay of Hogan to encompass the use of molecular torches of Becker. Becker teaches that there are numerous means for detecting probes designed to preferentially hybridize to the target sequence. Therefore, the method of Becker is an equivalent method as the method of Hogan which enables the detection of nucleic acid binding.

Response to Arguments

The response traverses the rejection. The response asserts that the Becker reference does not cure the deficiencies. This argument has been reviewed but is not convincing because the rejection of the previous rejection is maintained for the reasons presented above. Thus for the reasons above and those already of record, the rejection is maintained.

New Grounds of Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1, 11-21, 23, 29, 37-40, 50-53, 59-60, 84, 94-97, 114-116, 121-125, 133, 135, 137, 139, 141, 143, 151, 153, 155-156, 158 are rejected under 35 U.S.C. 112, first

paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to probes, primer and methods for detecting *Cryptosporidium parvum*.

The specification has provided specific sequences of SEQ ID NO: 6, 29, 48 for use in detecting *Cryptosporidium parvum* but not nucleic acids derived from non-*Cryptosporidium parvum* organisms including *Cryptosporidium muris*, *Cryptosporidium baileyi* or *Cryptosporidium wrairi*.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2b 1111, clearly states that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the ‘written description’ inquiry, whatever is now claimed”. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the

court states that "An adequate written description of a DNA...' required a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, there is no actual reduction to practice of the claimed invention, clear depiction of the claimed invention in the drawings or complete detailed description of the structure. A review of the language of the claim indicates that the claim is drawn to a genus, i.e., any nucleic acid that minimally hybridizes to a nucleic acid derived from a *Cryptosporidium parvum* organism in a test sample having at least 80% complementary to the target sequence of SEQ ID NO: 1. The partial structure provided within the claim broadly encompasses variant 18S rRNA, homologous 18S rRNA and nucleic acid sequences yet to be discovered. There is substantial variability among the species of DNAs encompassed within the scope of the claims because a nucleic acid which hybridizes to a nucleic acid derived from a *Cryptosporidium parvum* organism in a test sample having at least 80% complementary to the target sequence of SEQ ID NO: 1 is only a fragment. A description of a genus of nucleic acids may be achieved by means of a recitation of a representative number of nucleic acids, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. Therefore, weighing all factors, 1) partial structure of the DNAs that hybridizes to a nucleic acid derived from a *Cryptosporidium parvum* organism in a

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test sample which is at least 80% complementary to the target sequence of SEQ ID NO: 1, 2) the breadth of the claim, 3) the lack of correlation between the structure and function; in view of the level of knowledge and skill in the art, one skilled in the art would not recognize from the disclosure that the applicant was in possession of the genus of nucleic acids hybridizes to a nucleic acid derived from a *Cryptosporidium* organism in a test sample which is at least 80% complementary to the target sequence of SEQ ID NO: 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1, 11, 11-23, 29, 37-40, 50-53, 59-60, 84, 93-99, 106-107, 114-126, 133-144, 151-159 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1, 11-23, 29, 37-40, 50-53, 59-60, 84, 93-99, 106-107, 114-126, 133-144, 151-159 has been amended to require a target binding region, a target sequence, a target nucleic acid and a test sample. It is entirely confusing what is required to hybridize and bind to which target sequences or binding regions. First, the claim has been amended to be a probe comprising a target binding region from 18-35 bases in length where the target sequence is SEQ ID NO: 6, 10, 14, 18. Based upon the newly added claim language, it appears as though the target binding region may not be greater in length than SEQ ID NO: 6, 10, 14, 18, as the probe would then comprise a

base region in addition to said target binding region that would be capable of stably binding to said target. Since SEQ ID NO: 6, 10, 14, 18 are only 22 nucleotides in length, it is unclear how the probe target binding region is between 23-35 bases in length. It is noted that the range of 18-22 does not appear to be part of the originally filed disclosure. Similarly, the rejection is applicable to Claim 23 and the dependants thereof.

Conclusion

12. No claims allowable.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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14. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.


A) Rochelle et al. (Applied and Environmental Microbiology, Vol. 63, No. 1, pages 106-114, January 1997) teaches a method of using primers to the 18S to distinguish between *Crptosporidium parvum* and *Giardia lamblia* in water.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Jeanine Goldberg
Patent Examiner
March 4, 2004


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